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Research Article

Formulation and Evaluation of Immediate Release Bilayer Tablet of Sodium Alendronate and Calcium

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ABSTRACT

Sodium alendronate has been the most widely used drug for the treatment of osteoporosis especially postmenopausal women for many decades. The present investigation concerns the development and evaluation of bilayer oral tablet of sodium alendronate with calcium containing formulation for the treatment of osteoporosis thereby the patient related compliance is reduced and also to make cost effective product. A bilayer tablets was developed using excipients of micro-crystalline cellulose powder, stearic acid, starch and magnesium stearate, lake of erythrosine. The prepared tablets were evaluated in terms of their precompression parameters, physical characteristics and also in vitro release studies as per Indian Pharmacopeia specification. The results of the in vitro release studies showed that the optimized formulation could release the drug 95.8% for 45 hours. Optimized formulation showed no significant change in physical appearance, drug content and also in vitro dissolution study. Finally, the tablet formulations found to be economical and may overcome the draw backs associated with the drug during its absorption.

INTRODUCTION:

The oral route of drug administration is the most convenient, commonly used method of drug delivery and tablets of various types still the ruling dosage form since years [1]. Osteoporosis is defined as the type of systemic disease by reduced bone strength or mass. Drugs of choice in chronic treatment of osteoporosis are biphosphonates and its analogs. Sodium alendronate (ALD) is a second generation bisphosphonate derivative and antiresorptive drugs and it was new first-line agent recommended in the therapy of postmenopausal osteoporosis and it potently inhibits bone resorption. ALD was the first compound registered as the anti-fracture agent category as well as most prescribed drug for the osteoporosis. ALD are known to increase the bone mineral density by inhibiting the osteoclast-mediated bone resorption and thereby reduce the risk of fractures. ALD plays a sustained reduction in the levels of biochemical markers of bone remodeling, returning them to the premeno-pausal range. Alendronate sodium tablets are indicated for treatment to increase bone mass in men with osteoporosis and also for the prevention of postmenopausal osteoporosis in women. Moreover, Alendronate sodium tablets are indicated for the treatment of Paget's disease of bone in men and women. On the other hand, calcium is the one of the essential minerals for bone strength. Calcium may also reduce the loss of bone mineral in post-menopausal women [2]. Bone mineral density (BMD) or incidence of osteoporotic bone fractures can be changed by the combination of calcium and vitamin D. The combination of calcium and Sodiumalendronate can be effective in the prevention and treatment of osteoporosis in adults [3,4].

The main purpose of this research work was to design and develop bilayer tablet formulation for osteoporosis especially for postmenopausal women by direct compression method using excipients and to compare the tablet properties with IP specification. The blend was compressed on a tablet punching machine, tablets were subjected to various tests (weight variation, diameter and thickness, hardness, disintegration and assay of the drug) and the results were also in compliance with the official specifications.

RESEARCH DESIGN AND METHODS

Materials

Sodium alendronate (ALD) is gift sample from Intermed Pharma, Chennai. All chemicals and excipients used in this research work were procured from commercial source and were of analytical and pharmaceutical grade.

Formulation design

ALD layer

Bilayer tablet were formulated by non-granulation technique of direct compression method as per the formula given in Table-1. Initially required quantity of API was passed through the sieve number #40 separately after that pre-weighed stearic acid was crushed and passed into #40mesh, followed by microcrystalline cellulose PH 103. Starch was passed into #100 mesh separately, finally magnesium stearate was passed into the #100 mesh separately. Blending were carried out by manually with the help of poly bag by shaking shifted material of ALD, micro-crystalline cellulose PH 103, stearic acid, starch for 15 minutes. After that shifted magnesium stearate was added in that dry mixed powder to improve the flow behavior of powder blend, finally lake of erythrosine was added and again blended untilcolor was distributed properly [5].

Calcium layer

Calcium layer were prepared by same procedure carried out in ALD layer with some modification. Here calcium is used in the form of calcium carbonate, initially calcium layer excipients were weighed and taken for shifting, before that stearic acid was weighed and crushed in mortar, followed by passing into the #40mesh, after that micro-crystalline cellulose passed separately in #40 mesh and starch, magnesium stearate were passed into the #100 mesh. All the shifted materials were taken into a poly bag except magnesium stearate. Blending process was carried out by manual for 15 minutes. After dry mixing, magnesium stearate was added to lubricate the blended powder to enhance the flow property of powder from hopper into punch lower die cavity to avoid improper filling[6].The detail of composition of the formulation is given in Table 1.

Table 1. Formulations excipients used per tablet

Sodium alendronate layer	Quantity used	Calcium layer	Quantity used
Sodium Alendronate	100 mg	Calcium carbonate (Equivalent to calcium)	50 mg
Microcrystalline cellulose powder PH 101	30 mg	Microcrystalline cellulose powder PH 101	20 mg
Stearic acid	0.5 mg	Stearic acid	5mg
Starch	24.5 mg	Starch	15 mg
Lake of erythrosine	quantity sufficient		

Both lubricated blend was tested for blend parameter of bulk density, tapped density, compressibility index, and Hausner's ratio. Results of pre-compression parameter was clearly represented in Table 2.

Table 2. Physical property characterization

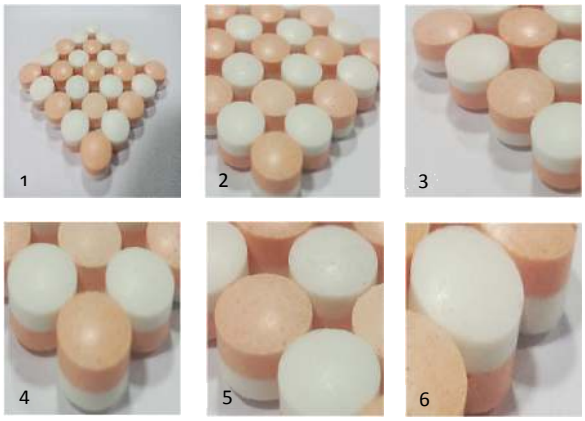
S.No.	Characterization	Results
For Sodium Alendronate Layer		
1	Bulk density (gms/ml)	0.5584
2	Tap density (gms/ml)	0.5421
3	Compressibility index (%)	18.0162
4	Hausner's ratio	1.2017
5	Flow character	Fair
For Calcium Layer		
1	Bulk density (gms/ml)	0.4245
2	Tap density (gms/ml)	0.4967
3	Compressibility index (%)	14.56
4	Hausner's ratio	1.04
5	Flow character	Fair

Figure-1 *Picture representing bilayer tablet*

Compression of bilayer tablet formulation

Each lubricated blend was loaded into the separate hopper and the tablet were compressed into a tablet using 24-station Inwika double hopper tablet compression machine with flat faced without any engrave and debossing, in the dimension of 0.55mm width and 0.7mm diameter, with 15 RPM speed. Compressed tablet was depicted in the Figure 1 and Figure 2.

Figure-2 *Group of zoomed pictures of bilayer tablet*



Evaluation of bilayer tablet formulation

General appearance

Visual identity is important thing of tablet formulation. Good appearance make attraction to buy a medicine. Visual observation was done and appearance of tablet formulation shown in the form of pictorial representation in Figure-1 andFigure-2.

Dimension of tablet

Dimension of tablet includes thickness. Thickness plays an important role in the tablet formulation. Uneven thickness of tablet cannot fit into the blister packing cavity of tablet. Thickness of the tablet measured with the help of digital screw gauge and data was documented.

Weight uniformity

Pooled random sample was taken from compressed bulk tablet. Twenty tablet individual weights were checked and noted. Uniformity of tablet was calculated by standard methods for positive and negative deviations. The percentage (%) difference in the weight variation should be within the acceptable limits (±7.5%). The percentage (%) deviation was calculated using the following formula.

$$\text{Negative deviation} = \frac{\text{Miw} - \text{Aw} \times 100}{\text{Aw}}$$

$$\text{Positive deviation} = \frac{\text{Maw} - \text{Aw} \times 100}{\text{Aw}}$$

Where Miw = Minimum weight, Aw = Average weight, Maw = Maximum weight

Hardness (crushing strength)

Crushing strength of tablet is key factor in the formulation of oral solid dosage form. Hardness less than 4 kp results patient handling problem, while transportation tablet will breakdown easily so patient cannot able to take. Hardness of tablet were measured using ervika hardness tester, data was recorded and documented.

Friability

Friability is another one quality parameter in tablet formulation. As per USP the tablets equivalent to 6.5 gram subjected into friability test. Friability of tablet was determined by Rocha friability tester. A sample of pre-weighed tablets was placed in friabilator. The friabilator apparatus was operated for 100 revolutions after that tablet was de-dusted by lint free cloth and weighted. Percentage (%) friability was calculated by initial weight minus final weight of de-dusted tablet multiplied with 100 and divided by initial weight of tablet

Disintegration

This test assuring whether the tablet disintegrating or not in a liquid medium at the specified time of 15 minutes with prescribed experimental condition. 6 tablets were randomly selected to test the disintegration time of tablet. Each tablet were placed in a disintegration basket -1 (As per USP) at each tube made of transparent open end cylinder with one end covered by stainless steel wire mesh in range of 1.8-2.2 mm and above assembly was placed in 1000 ml water containing basket- rack assembly at 37±2^{0}C. Disintegration test was carried out until tablet particle passes through the sieve no #10. Disintegration date of formulated tablet were recorded and documented [7]. The evaluation results of the tablet formulations are shown in Table 3.

Table 3. Evaluation of formulated tablets

S.No.	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegartion Time (minutes)
1	253.5± 0.02	4.58	7.5	0.09	6 min 49 sec
2	251.9± 0.03	4.51	7.3	0.08	7 min 5 sec
3	248.9± 0.03	4.49	7.4	0.07	6 min 48 sec
4	250.4± 0.04	4.57	7.9	0.08	6 min 59 sec
5	250.7± 0.03	4.56	8	0.09	6 min 56 sec
6	254.6± 0.03	4.54	7.8	0.07	7 min 2 sec
7	251.1± 0.05	4.51	7.4	0.08	6 min 56 sec
8	253.6± 0.03	4.58	7.1	0.09	7 min 2 sec
9	249.6± 0.02	4.56	7.5	0.07	7 min 5 sec
10	253.9± 0.04	4.49	7.8	0.09	7 min 3 sec

***In-vitro* drug release study**

Apparatus : USP dissolution apparatus I (Paddle type)

Temperature (^{0}C) : 37^{0}C ±2^{0}C

RPM : 50 rpm

Dissolution media : Water

Media volume : 900 ml

Buffer solution:

14.7 g of sodium citrate dihydrated and 7.05g of anhydrous disodium hydrogen phosphate were dissolved in 900ml water, pH of the water was adjusted using orthophosphoric acid and diluted up to 1000ml.The above solution was filter into 0.45 micron filter.

Diluent:

14.7 gm of sodium citrate dihydrate were dissolved in 500 ml of water.

Borate solution:

3.1 gm of boric acid was dissolved in 475 ml of water and the pH was adjusted by 1N sodium hydroxide and the solution was diluted up to 500 ml.

0.05% 9-fluoroenmethylchloroformate solution:

50 mg of 9-fluoroenmethylchloroformate were dissolved in acetonitrile in 100 ml volumetric flask.

Reference solution: 50 mg reference standard of ALD was dissolved in 50 ml of volumetric flask with dissolution media and from that one ml of solution was taken, dissolved in 10 ml volumetric flask containing dissolution media. From that 5ml of solution was transformed into centrifuge tube. 5 ml of borate solution, 4 ml of 9-fluoroenmethylchloroformate solution and 25 ml of methylene chloride were added into the centrifuge tube containing 5 ml of reference solution fallowed by centrifuge tube was placed in a centrifuge apparatus. Centrifugation process was carried until the solution was clear.

Mobile phase : 75:20:5 v/v/v of Buffer: Acetonitrile: Methanol

Column : Polymer X, 10 micron.

Flow rate : 1 ml

Injection volume : 50 micro liter

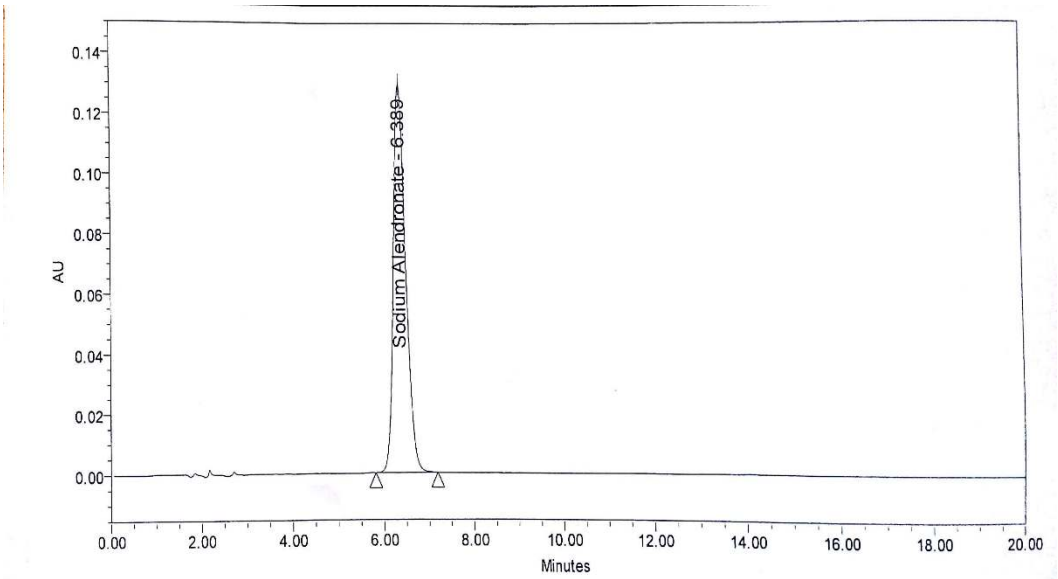
Pump : Isocratic

The prepared bi-layer tablets were placed in 900 ml of dissolution media and the temperature of the medium was maintained at $37^0 \pm 2^0$C. Dissolution study was carried out for 45 minutes. 10 ml of sample solution were taken from the dissolution jar at each sampling point and 10 ml of dissolution mediawas replaced in a dissolution jar in order to maintain sink condition. Final solution was filtered by using whatmann filter paper and 5 ml of filter solution was transferred into centrifuge tube and 5 ml of borate solution, 4 ml of 9-fluoroenmethylchloroformate solution and 25 ml of methylene chloride were added into the centrifuge tube containing 5 ml of reference solution fallowed by centrifuge tube was placed in a centrifuge apparatus. Centrifugation process was carried until the solution was clear [8]. Percentage (%) drug release of ALD was calculated and tabulated in Table 4. Sample chromatogram was shown inFigure-3.Data plotted for the percentage of drug release Vs time is depicted in Figure-4.

Table 4. Results of In-vitro drug release study

S.No.	Time in minutes	Percentage drug release
1	5	25.9
2	10	48.9
3	15	64.6
4	20	74.8
5	30	83.1
6	45	95.8

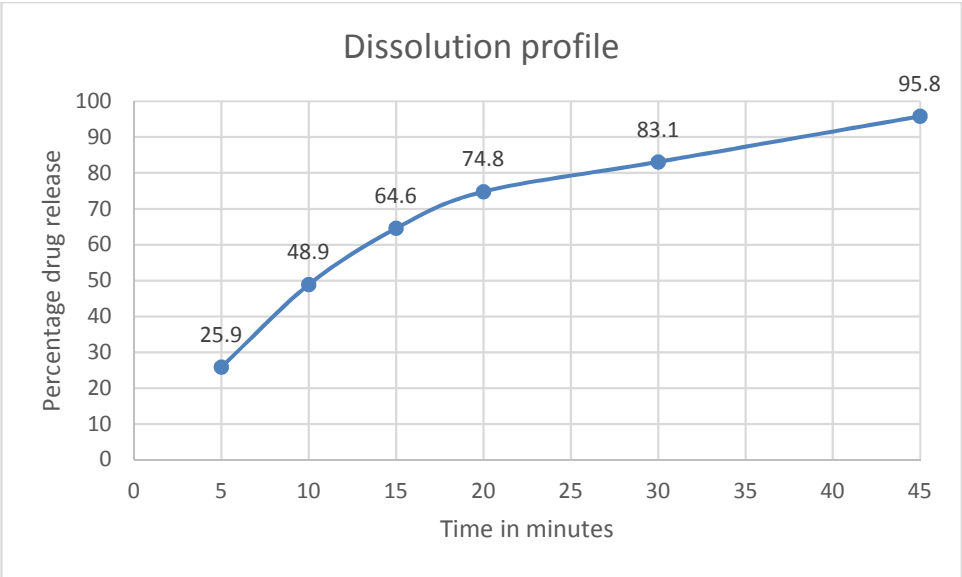
Figure-3 *HPLC Chromatogram of Sodium Alendronate*



Peak Results

	Retention Time (min)	Area (µV*sec)	Name	K Prime
1	6.39	2454133	Sodium Alendronate	2.7

Figure-4 *Percentage drug release Vs Time in minutes*



Assay

Assay of ALD was carried by RP-HPLC methods described in dissolution.

CONCLUSION

In this present work, an attempt had been made to design and develop an immediate release tablet using sodium alendronate with calcium for osteoporosis. The result depicting that optimized batch lubricated blend showing faire flow character and assay data expressing that blending time also optimized, sometime over blending time result uneven API distribution cause cannot complies official pharmacopeia and uneven lubricant distribution will affect tablet imperfection of weight variation, thickness variation, striking and picking. The general appearance of tablet represented in the form pictorial and it was pasted and labeled as Figure-1 &Figure-2. It was showing the double layer tablet with good attractive appearance and smooth edges without any embossing and Congreve, one layer was light orange in color, it indicates ALD layer, and another layer was white in color, as usual calcium carbonate color with same color excipients. The thickness (mm) of the formulated bi-layer tablet were found in range of 4.49 mm to 4.58 mm. The weight variation results present in the range of248.9 mg to 254.6 mg for bi-layer tablets indicating that the percentage (%) deviation in weight variation from average value for the formulated tablet were within limit. The crushing strength test was carried out using monsanto hardness tester. The crushing strength of the formulated tablets was found to be uniform and moreover within acceptance limit (6-8 kg/cm^2) the results assuring that the formulated bi-layer tablets not break while transportation. Friability was performed and results was found to be less than 1% and within specified limits, and it ensures that the ability of tablet to withstand shocks and also suitable for better shipment and transportation. Disintegration data was displayed in Table- 4 indicated that the formulated tablet has fast disintegration release and complies within standard limits. The *in vitro* drug release profiles of prepared bi-layer tablet are displayed in Table-5. It was shown that the maximum drug was released at the 45 minutes.98% and 102% of API (nimesulide) was found in the formulation and it showing ±3% variation and this value ensures good uniformity of the API content in the tablets.

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